



Improving the Quality of Care: Antipsychotic Use in Children and Adolescents

Key Points:

- Prescribing of antipsychotic medications to children and adolescents is increasing, despite a lack of safety data and a high risk of neurologic, psychiatric, and metabolic adverse effects.
- Antipsychotic medications should be prescribed for a specific clinical indication only when the scientific evidence supports the likelihood that benefits will exceed harms. For children and adolescents, use of antipsychotic medication for United States Food and Drug Administration (FDA)-approved indications generally implies more certainty that benefits will exceed risks, compared to off-label use. Prescribing beyond FDA-approved indications must be approached cautiously.
- No antipsychotics are FDA-approved for patients under three years of age. Only two older, first-generation antipsychotics are FDA-approved for patients under five years of age. FDA-approved indications for children under 10 years of age are very limited, especially among newer, second-generation antipsychotics.
- As of October 1, 2014, any use of antipsychotics for Medi-Cal beneficiaries 0 – 17 years of age requires an approved *Treatment Authorization Request* (TAR).
- Concurrent use of more than one antipsychotic medication is not recommended. Among all children and adolescents in the Medi-Cal fee-for-service population with at least 90 consecutive days of antipsychotic medication treatment, almost 6 percent were taking two or more antipsychotic medications concurrently for at least 90 consecutive days.
- Serious adverse effects are common with antipsychotic medication use, particularly weight gain, dyslipidemia, diabetes, and cardiovascular disease. While both baseline and periodic metabolic monitoring is recommended, only 37 percent of children and adolescents in the Medi-Cal fee-for-service population had appropriate metabolic testing during a one-year time period.
- Psychosocial care, which includes behavioral interventions, psychological therapies, and skills training, among others, remains the recommended first-line treatment option for children and adolescents for nonpsychotic conditions such as attention deficit disorder and disruptive behaviors. Antipsychotic medications, when prescribed, should be part of a comprehensive, multi-modal plan for coordinated treatment that includes psychosocial care.
- The safest use of antipsychotic medications in children and adolescents requires close, in-person clinical monitoring by prescribers for both clinical response and adverse neurologic, psychiatric, and metabolic effects.

Background

Prescribing of antipsychotic medications to children and adolescents has increased rapidly in recent decades, driven by new prescriptions and by longer duration of use.¹ The frequency of prescribing antipsychotics to children and adolescents increased almost fivefold from 1996 – 2002, from 8.6 per 1,000 to 39.4 per 1,000.² A national study found that prescribing of atypical antipsychotics increased 62 percent from 2002 – 2007 among children and adolescents enrolled in Medicaid.³

Although some clinical evidence supports the efficacy of antipsychotics in patients under 18 years of age for certain narrowly defined conditions, according to a 2011 report by the Agency for Healthcare Research and Quality (AHRQ), children taking antipsychotic medications receive an

atypical antipsychotic 90 percent of the time, and in the majority of patients the use is for an off-label indication, including attention deficit/hyperactivity disorder (ADHD) and aggressive behavior.⁴ One study found that in the Medicaid population, more than 3/4 of children and adolescents were taking antipsychotics for an indication that is not FDA approved.⁵ For reference, current FDA-approved indications for selected antipsychotic medications are listed in Table 1.

Table 1. Antipsychotic Medications: FDA-approved Indications for Children and Adolescents

	Age (years)							
	<1	1 – 2	3 – 4	5	6 – 9	10 – 11	12	13 – 17
Second-Generation (Atypical) Antipsychotics								
aripiprazole*	NONE				I,T	I,M,T		I,M,S,T
asenapine*	NONE					M		
clozapine*	NONE							
iloperidone*	NONE							
lurasidone*	NONE							
olanzapine*	NONE					D,M		D,M,S
paliperidone	NONE						S	
quetiapine*	NONE					M		M,S
risperidone*	NONE			I		I,M		I,M,S
ziprasidone*	NONE							
First-Generation (Typical) Antipsychotics								
chlorpromazine*	NONE	B						NONE
fluphenazine*	NONE							
haloperidol*	NONE		H,P,S,T					
loxapine*	NONE							
molindone*	NONE						S	
perphenazine*	NONE						S	
pimozide	NONE						T	
thioridazine*	NONE			S				
thiothixene*	NONE						S	
trifluoperazine*	NONE				S			

* As of the date of publication of this article, these drugs appear on the Medi-Cal List of Contract Drugs, although some medications have restrictions on manufacturer codes. For current information, use the online Medi-Cal Formulary search tool available at <http://www.dhcs.ca.gov/services/Pages/FormularyFile.aspx>.

Key:

B	Severe behavioral problems marked by combativeness and/or explosive hyperexcitable behavior and short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders
D	Acute depressive episodes associated with Bipolar I Disorder (along with fluoxetine)
H	Hyperactivity
I	Irritability associated with autism disorder
M	Manic or mixed episodes associated with Bipolar I Disorder
P	Psychosis
S	Schizophrenia
T	Tourette's Syndrome

While antipsychotic medications can be of significant benefit, these drugs also have serious common side effects, including weight gain, hyperprolactinemia, and metabolic disturbance,

which may result in children and adolescents developing into adults who struggle with obesity, diabetes, and dyslipidemias.⁶ In addition, serious neurologic side effects, such as tardive dyskinesia, are associated with both first- and second-generation antipsychotic medications.⁷ Even when used for approved indications, antipsychotic medications can complicate treatment by creating or unmasking additional psychiatric symptoms, including sedation, agitation, anxiety, and suicidal thinking and behavior.⁷ Therefore, antipsychotics should be prescribed for a specific clinical indication only when the scientific evidence supports the likelihood that benefits will exceed harms, and the risk of treatment should be considered and periodically re-evaluated for each individual patient. Considering that atypical antipsychotics already have the greatest mean prescription cost of any psychotropic medication and are the most costly drug class within the Medicaid program, the additional costs associated with potential long-term treatment of chronic diseases makes it even more important for providers to carefully balance the economic and medical consequences with the potential benefits of treatment.^{5,8}

In addition, a recent systematic review found that among children and adolescents prescribed any antipsychotic, 10 percent were taking multiple concurrent antipsychotics.⁹ One study of a large state Medicaid fee-for-service program found that approximately seven percent of children 6 – 17 years of age taking any antipsychotic were prescribed two or more antipsychotics for longer than 60 days.¹⁰ These rates are of particular concern given that none of the American Academy of Child & Adolescent Psychiatry (AACAP) practice parameters recommend concurrent use of multiple antipsychotic medications, due to a lack of high-quality studies on the side effects and clinical efficacy of multiple concurrent antipsychotics.^{11,12}

Measuring Quality Care: Safe and Judicious Use of Antipsychotics in Children and Adolescents

For 2015, the National Committee for Quality Assurance (NCQA) Healthcare Effectiveness Data and Information Set (HEDIS[®]) added the following three new measures focused on the safe and judicious use of antipsychotic medications in children and adolescents:¹³

1. Metabolic Monitoring for Children and Adolescents on Antipsychotics (APM), which assesses the percentage of children and adolescents who have ongoing use of antipsychotic medications and metabolic testing during the measurement year. AACAP practice parameters for the use of atypical antipsychotic medications in children and adolescents state:
 - “The acute and long-term safety of these medications in children and adolescents has not been fully evaluated and therefore careful and frequent monitoring of side effects should be performed...Ideally, monitoring of BMI, blood pressure, fasting blood glucose and fasting lipid profiles should follow, whenever feasible, the recommendations found in the consensus statement put forth by the American Diabetes Association and the American Psychiatric Association.” (Recommendation 10, Clinical Guideline).¹¹

Table 2. American Diabetes Association Screening Guidelines for Patients on Second-Generation Antipsychotics¹⁴

	Baseline	4 weeks	8 weeks	12 weeks	Annually
Personal & family history	X				X
Weight (BMI)	X	X	X	X	
Waist circumference	X				X
Blood pressure	X			X	X
Fasting plasma glucose	X			X	X
Fasting lipid profile	X			X	

- “Careful attention should be given to the increased risk of developing diabetes with the use of atypical antipsychotic agents (AAA), and blood glucose levels and other parameters should be obtained at baseline and monitored at regular intervals.” (Recommendation 12, Clinical Standard).¹¹

- “In those patients with significant weight changes and/or a family history indicating high risk, lipid profiles should be obtained at baseline and monitored at regular intervals.” (Recommendation 13, Clinical Guideline).¹¹
2. Use of Multiple Concurrent Antipsychotics in Children and Adolescents (APC), which assesses the percentage of children and adolescents who were taking two or more concurrent antipsychotics for at least 90 days during the measurement year. AACAP practice parameters for the use of atypical antipsychotic medications in children and adolescents state:
- “The simultaneous use of multiple AAA has not been studied rigorously and generally should be avoided.” (Recommendation 8, Not Endorsed).¹¹
3. Use of First-line Psychosocial Care for Children and Adolescents on Antipsychotics (APP), which assesses the percentage of children and adolescents who had a new prescription for an antipsychotic medication without a primary indication for it and had documentation of psychosocial care as first-line treatment. AACAP practice parameters for the use of atypical antipsychotic medications in children and adolescents state:
- “Prior to the initiation of and during treatment with an AAA, the general guidelines that pertain to the prescription of psychotropic medications should be followed.” (Recommendation 1, Clinical Standard).¹¹
 - “When selecting any AAA for use in a child or adolescent, the clinician should follow the most current available evidence in the scientific literature.” (Recommendation 2, Clinical Standard).

Medi-Cal Policy Aligns with Clinical Guidelines

- Medi-Cal has always required an approved TAR for the use of antipsychotics for non-FDA approved indications, and for any use in children less than 6 years of age. Of note, it was found that requiring an approved TAR for non-FDA approved indications was often difficult to enforce.
- Since May 1, 2012, antipsychotic use for Medi-Cal beneficiaries 6 – 17 years of age has been restricted to the use of one antipsychotic, except during titration period and, within this age group, concurrent use of two or more antipsychotics has required an approved TAR.
- As of October 1, 2014, **any** use of antipsychotics for Medi-Cal beneficiaries 0 – 17 years of age requires an approved TAR. For additional information about this policy, a Frequently Asked Questions (FAQ) document is available on the California Department of Health Care Services Pharmacy Benefits Division website at <http://www.dhcs.ca.gov/services/Pages/PharmacyBenefits2.aspx>.

Antipsychotic Use Among Children and Adolescents in the Medi-Cal Fee-for-Service Population

A retrospective cohort study was conducted to evaluate two of the HEDIS performance measures for antipsychotic medication use among children and adolescents (APM and APC) in the Medi-Cal fee-for-service population, using medical and pharmacy claims data. Study population selection criteria were adapted from HEDIS performance indicators and included all Medi-Cal beneficiaries who met the following inclusion criteria:

- Continuously eligible beneficiary enrolled in the Medi-Cal fee-for-service program for the duration of the measurement year (October 1, 2013, through September 30, 2014)
- 1 – 17 years of age as of September 30, 2014
- At least one paid pharmacy claim for an antipsychotic medication during the measurement year

Descriptive statistics were used to summarize beneficiary characteristics and HEDIS rates. Data were stratified into three age groups, per HEDIS specifications.

Results

A total of 6,688 Medi-Cal fee-for-service beneficiaries met the inclusion criteria, and within this group there were a total of 58,598 paid claims for antipsychotic medications. Demographic characteristics of the beneficiaries are listed in Table 3 including gender and race/ethnicity.

Table 3. Demographic Characteristics of the Medi-Cal Fee-for-Service Study Population

	1 – 5 years	6 – 11 years	12 – 17 years
Overall Population (n = 6,688)	82 (1%)	2,038 (30%)	4,568 (68%)
Gender			
Male (n = 4,349; 65%)	61 (74%)	1,409 (69%)	2,879 (63%)
Female (n = 2,339; 35%)	21 (26%)	629 (31%)	1,689 (37%)
Race/Ethnicity			
White/Caucasian, non-Hispanic (n = 3,173; 47%)	29 (35%)	924 (45%)	2,220 (49%)
All other races/ethnicities (n = 3,515; 53%)	53 (65%)	1,114 (55%)	2,348 (51%)

The study population was almost 2/3 male (n = 4,439; 65%) and almost half of these beneficiaries identified as white/Caucasian race, non-Hispanic ethnicity (n = 3,173; 47%).

Overall rates for APM (Table 4) and APC (Table 5), as well as rates stratified by the three age groups are listed below. Of note, for the APM calculation, a total of 675 beneficiaries were excluded as they only had one paid claim for an antipsychotic medication during the measurement year (leaving a denominator of 6,013 beneficiaries) and, for the APC calculation, a total of 1,313 beneficiaries were excluded as they had less than 90 days of continuous antipsychotic medication treatment during the measurement year (leaving a denominator of 5,375 beneficiaries).

Table 4. Metabolic Monitoring in Children and Adolescents with ≥2 Paid Claims for Antipsychotic Medications During the Measurement Year (October 1, 2013, through September 30, 2014)

Age Group	Numerator Children and adolescents with ≥1 test for both blood glucose/HbA1C and LDL-C/cholesterol	Denominator Children and adolescents with ≥2 paid claims for antipsychotic medications	Percentage of children and adolescents with ≥2 paid claims for antipsychotic medications and metabolic testing
1 – 5 years	18	68	26.5%
6 – 11 years	575	1,838	31.3%
12 – 17 years	1,653	4,107	40.2%
TOTAL	2,246	6,013	37.4%

Although the 37.4 percent figure calculated using HEDIS measure parameters gives the rate at which both tests were completed (blood glucose or HbA1C and LDL-C or cholesterol), individual testing rates were also calculated for the study population. The rate of glucose or Hb1AC monitoring (n = 3,151; 52.4%), was much greater than LDL-C or cholesterol monitoring

(n = 2,279; 37.9%), suggesting there is an opportunity for outreach to providers, who could raise the metabolic monitoring rate calculated in the HEDIS measure by ordering both tests at the same time.

Of note, the HEDIS documentation for this measure included an analysis using the 2008 Medicaid Analytic eXtract (MAX) data files. These data showed an average metabolic monitoring rate across data collected from 11 states of 18.5 percent (range: 4.8 percent – 36.2 percent), more than half the rate found in the Medi-Cal fee-for-service population.¹³

Table 5. Children and Adolescents on Multiple Concurrent Antipsychotic Medications During the Measurement Year (October 1, 2013, through September 30, 2014)

Age Group	Numerator Children and adolescents on ≥2 concurrent antipsychotic medications ≥90 consecutive days	Denominator Children and adolescents with ≥90 consecutive days of antipsychotic medication treatment	Percentage of children and adolescents on ≥2 concurrent antipsychotic medications
1 – 5 years	0	53	0.0%
6 – 11 years	61	1,665	3.7%
12 – 17 years	245	3,657	6.7%
TOTAL	306	5375	5.7%

This calculated rate of 5.7 percent of Medi-Cal fee-for-service beneficiaries on multiple concurrent antipsychotic medications is close to the published rates for this measure found in the HEDIS documentation, which used the 2008 MAX data files and found average rate of 6.0 percent across 11 states (range: 2.8 percent – 9.4 percent).¹³

Within the 306 beneficiaries identified on greater than two concurrent antipsychotic medications for at least 90 consecutive days, concurrent use of aripiprazole, risperidone, and/or quetiapine accounted for 65.4 percent of concurrent antipsychotic medication use, including concurrent use of risperidone-aripiprazole (n = 70), quetiapine-aripiprazole (n = 68), quetiapine-risperidone (n = 62).

Clinical Recommendations

- Psychosocial care, which includes behavioral interventions, psychological therapies, and skills training, among others, is the recommended first-line treatment option for children and adolescents diagnosed with nonpsychotic conditions such as attention-deficit disorder and disruptive behaviors.
- Prior to the initiation of treatment with antipsychotic medication, obtain a personal and family history of diabetes and hyperlipidemia, seizures and cardiac abnormalities, as well as any family history of previous response or adverse events associated with antipsychotic medication.
- When prescribed, antipsychotic medications should be part of a comprehensive, multi-modal plan for coordinated treatment that includes psychosocial care.
- Antipsychotic dosing should follow the “start low and go slow” approach and seek to find the lowest effective dose. Determination of an appropriate target dose should follow both the current scientific literature and the clinical response of the patient, while also monitoring the patient for side effects and tolerability. Multiple clinical guidelines suggest that higher than approved dosages of antipsychotic medications should be avoided.¹⁴
- Periodically review the ongoing need for continued therapy with antipsychotic medications.

- Monitor BMI, blood pressure, fasting blood glucose, and fasting lipid profiles according to the recommendations found in the consensus statement put forth by the American Diabetes Association and the American Psychiatric Association.
- Periodically review AACAP practice parameters for updated information on the AACAP website at http://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx.
- Review additional prescriber resources developed by the Ohio Psychotropic Medication Quality Improvement Collaborative, including a psychotropic medication contraindications and interactions table, atypical antipsychotics adverse effects table, and a screening and monitoring tool available at their website at http://www.ohiomindsmatter.org/Prescribers_Psychotropic.html.

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